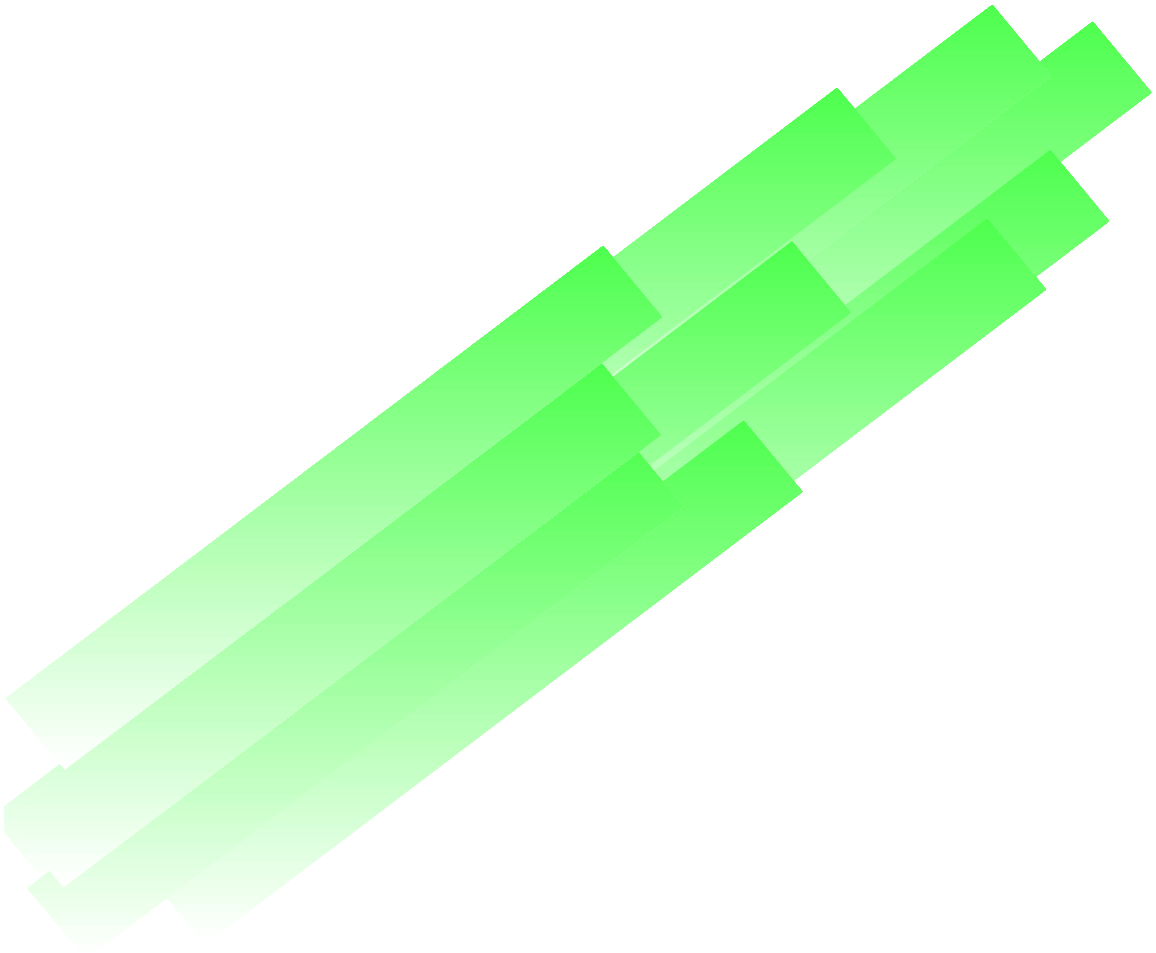
Guidance for Industry

Labeling Guidance for Astemizole Tablets



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
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GUIDANCE FOR INDUSTRY[1]

Labeling Guidance for Astemizole Tablets

I. INTRODUCTION

This guidance describes the recommended labeling to comply with 21 CFR 314.94(a)(8)(iv) for an abbreviated new drug application. The basis of this guidance is the approved labeling of the reference listed drug (HISMANAL®; Janssen Pharmaceutica; 19-402/S-009; Approved February 9, 1996; Revised February 1996). Differences between the reference listed drug and this guidance may exist and may include differences in expiration date, formulation, bioavailability, or pharmacokinetics, or omission of an indication or other aspects of labeling protected by patent or accorded exclusivity under section 505(j)(4)(D) of the Federal Food, Drug, and Cosmetic Act.

II. LABELING

ASTEMIZOLE TABLETS

DESCRIPTION

Astemizole is a histamine H_1-receptor antagonist. Astemizole is chemically designated as 1-(*p*-Fluorobenzyl)-2-[[1-(*p*-methoxyphenethyl)-4-piperidinyl]amino]benzimidazole. Astemizole is a white to slightly off-white powder; it is insoluble in water, slightly soluble in ethanol and soluble in chloroform and methanol. It has a molecular weight of 458.58. The molecular formula is $C_{28}H_{31}FN_4O$. It has the following structural formula:

[INSERT STRUCTURAL FORMULA HERE]

Each tablet for oral administration, contains 10 mg of astemizole. In addition, each tablet contains the following inactive ingredients: *[Please note that in accordance with good pharmaceutical practice, all dosage forms should be labeled to cite all the inactive ingredients (refer to USP General Chapter <1091> for guidance).]*

CLINICAL PHARMACOLOGY

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[1]This guidance has been prepared by the Office of Generic Drugs, Division of Labeling and Program Support in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance represents the Agency's current thinking on the development of labeling for an abbreviated new drug application. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirement of the applicable statute, regulations, or both.

Astemizole is a long-acting, selective histamine H_1-receptor antagonist. Receptor binding studies in animals demonstrated that at pharmacological doses, astemizole occupies peripheral H_1-receptors but does not reach H_1-receptors in the brain. Whole body autoradiographic studies in rats, radiolabel tissue distribution studies in dogs and radioligand binding studies of guinea pig brain H_1-receptors have shown that astemizole does not readily cross the blood-brain barrier. Screening studies in rats at effective antihistaminic doses showed no anticholinergic effects. Studies in humans using the recommended dosage regimens have not been performed to determine whether astemizole is associated with a different frequency of anticholinergic effects than therapeutic doses of other antihistamines.

The absorption of astemizole is reduced by 60% when taken with meals. In single oral dose studies, astemizole was rapidly absorbed from the gastrointestinal tract; peak plasma concentrations of unchanged astemizole were reached within one hour. Due to extensive first pass metabolism and significant tissue distribution, plasma concentrations of unchanged drug were low. Elimination of unchanged astemizole occurred with a half-life of approximately one day. Elimination of astemizole plus hydroxylated metabolites, considered together to represent the pharmacologically active fraction in plasma, was biphasic with half-lives of 20 hours for the distribution phase and 7 to 11 days for the elimination phase. The pharmacokinetics of astemizole plus hydroxylated metabolites are dose proportional following single doses of 10 mg to 30 mg.

Following chronic administration, steady state plasma concentrations of astemizole plus hydroxylated metabolites (mainly desmethylastemizole) were reached within four to eight weeks; concentrations of the metabolites are substantially higher than those of unchanged astemizole. Astemizole plus hydroxylated metabolites decayed biphasically with an initial half-life of 7 to 9 days, with plasma concentrations being reduced by 75% within this phase, and with a terminal half-life of about 19 days. The initial phase ($t_{1/2}$ = 7 to 9 days) appears to determine the time to reach steady state plasma concentrations of astemizole plus hydroxylated metabolites. Steady state plasma concentrations of unchanged astemizole were reached by 6 days (with a range of 6 to 9 days); unchanged astemizole was eliminated from plasma with a half-life of approximately 2 days (with a range of 1 to 2.5 days).

Excretion and metabolism studies with ^{14}C-labeled astemizole in volunteers demonstrated that the drug is almost completely metabolized in the liver and primarily excreted in the feces.

Interpatient variability in pharmacokinetic parameters may be greater in patients with liver disease as compared to normal subjects. Systematic evaluation of the pharmacokinetics in patients with hepatic or renal dysfunction has not been performed.

The *in vitro* plasma protein binding of unchanged astemizole (100 ng/mL) was 96.7% with 2.3%

being found as free drug in the plasma water. In human blood with an astemizole concentration of 100 ng/mL, 61.5% of astemizole was bound to the plasma proteins, with 36.2% being distributed to the blood cell fraction. The concentration of astemizole found in the blood was the same as that found in the plasma fraction of the blood. Binding studies for the astemizole metabolite(s) which achieve much higher concentrations than astemizole under chronic dosing conditions have not been conducted.

INDICATIONS AND USAGE

Astemizole tablets are indicated for the relief of symptoms associated with seasonal allergic rhinitis and chronic idiopathic urticaria. Astemizole should not be used as a prn product for immediate relief of symptoms. Patients should be advised not to increase the dose in an attempt to accelerate the onset of action.

Clinical studies have not been conducted to evaluate the effectiveness of astemizole tablets in the common cold.

CONTRAINDICATIONS

CONCOMITANT ADMINISTRATION OF ASTEMIZOLE WITH ERYTHROMYCIN IS CONTRAINDICATED BECAUSE ERYTHROMYCIN IS KNOWN TO IMPAIR THE CYTOCHROME P450 ENZYME SYSTEM WHICH ALSO INFLUENCES ASTEMIZOLE METABOLISM. THERE HAVE BEEN TWO REPORTS TO DATE OF SYNCOPE WITH TORSADES DE POINTES, REQUIRING HOSPITALIZATION, IN PATIENTS TAKING COMBINATIONS OF ASTEMIZOLE 10 MG DAILY WITH ERYTHROMYCIN. IN EACH CASE THE QT INTERVALS WERE PROLONGED BEYOND 650 MILLISECONDS AT THE TIME OF THE EVENT; ONE PATIENT ALSO RECEIVED KETOCONAZOLE AND THE OTHER PATIENT ALSO HAD HYPOKALEMIA.

CONCOMITANT ADMINISTRATION OF ASTEMIZOLE WITH KETOCONAZOLE TABLETS IS CONTRAINDICATED BECAUSE AVAILABLE HUMAN PHARMACOKINETIC DATA INDICATE THAT ORAL KETOCONAZOLE SIGNIFICANTLY INHIBITS THE METABOLISM OF ASTEMIZOLE, RESULTING IN ELEVATED PLASMA LEVELS OF ASTEMIZOLE AND DESMETHYLASTEMIZOLE. DATA SUGGEST THAT CARDIOVASCULAR EVENTS ARE ASSOCIATED WITH ELEVATION OF ASTEMIZOLE AND/OR ASTEMIZOLE METABOLITE LEVELS, RESULTING IN ELECTROCARDIOGRAPHIC QT PROLONGATION.

CONCOMITANT ADMINISTRATION OF ASTEMIZOLE WITH ITRACONAZOLE IS ALSO CONTRAINDICATED BASED ON THE CHEMICAL RESEMBLANCE OF ITRACONAZOLE AND KETOCONAZOLE. *IN-VITRO* DATA SUGGEST THAT ITRACONAZOLE HAS A LESS PRONOUNCED EFFECT ON THE BIOTRANSFORMATION SYSTEM RESPONSIBLE FOR THE METABOLISM OF ASTEMIZOLE COMPARED TO KETOCONAZOLE.

CONCOMITANT ADMINISTRATION OF ASTEMIZOLE WITH QUININE IS CONTRAINDICATED BECAUSE HUMAN DATA INDICATE THAT ADMINISTRATION OF QUININE (SINGLE DOSE OF 430 MG) WITH ASTEMIZOLE RESULTS IN ELEVATED PLASMA LEVELS OF ASTEMIZOLE AND DESMETHYLASTEMIZOLE WHICH IS ACCOMPANIED BY ELECTROCARDIOGRAPHIC QT PROLONGATION. THESE DATE ALSO INDICATE THAT, ALTHOUGH BEVERAGES CONTAINING QUININE (UP TO 80 MG/DAY OR ABOUT 32 OUNCES OF TONIC WATER) MAY ELEVATE PLASMA LEVELS OF ASTEMIZOLE AND DESMETHYLASTEMIZOLE, THIS EFFECT IS SMALL AND IS NOT ACCOMPANIED BY SIGNIFICANT PROLONGATION OF THE QT INTERVAL.

(See WARNINGS and PRECAUTIONS: Drug Interactions.)

Astemizole is contraindicated in patients with known hypersensitivity to astemizole or any of the inactive ingredients.

WARNINGS

QT PROLONGATION/VENTRICULAR ARRHYTHMIAS

RARE CASES OF SERIOUS CARDIOVASCULAR ADVERSE EVENTS INCLUDING DEATH, CARDIAC ARREST, QT PROLONGATION, TORSADES DE POINTES, AND OTHER VENTRICULAR ARRHYTHMIAS HAVE BEEN OBSERVED IN PATIENTS EXCEEDING RECOMMENDED DOSES OF ASTEMIZOLE. WHILE THE MAJORITY OF SUCH EVENTS HAVE OCCURRED FOLLOWING SUBSTANTIAL OVERDOSES OF ASTEMIZOLE, TORSADES DE POINTES (ARRHYTHMIAS) HAVE VERY RARELY OCCURRED AT REPORTED DOSES AS LOW AS
20 MG TO 30 MG DAILY (2 to 3 TIMES THE RECOMMENDED DAILY DOSE). DATA SUGGEST THAT THESE EVENTS ARE ASSOCIATED WITH ELEVATION OF ASTEMIZOLE AND/OR ASTEMIZOLE METABOLITE LEVELS, RESULTING IN ELECTROCARDIOGRAPHIC QT PROLONGATION.

THESE EVENTS HAVE ALSO OCCURRED AT 10 MG DAILY IN A FEW PATIENTS WITH POSSIBLE AUGMENTING CIRCUMSTANCES (SEE CONTRAINDICATIONS, AND WARNING PARAGRAPHS BELOW WARNINGS BOX). IN VIEW OF THE POTENTIAL FOR CARDIAC ARRHYTHMIAS, ADHERENCE TO THE RECOMMENDED DOSE SHOULD BE EMPHASIZED.

DO NOT EXCEED THE RECOMMENDED DOSE OF 10 MG (ONE TABLET) DAILY.

SOME PATIENTS APPEAR TO INCREASE THE DOSE OF ASTEMIZOLE IN AN ATTEMPT TO ACCELERATE THE ONSET OF ACTION. PATIENTS SHOULD BE ADVISED NOT TO DO THIS AND NOT TO USE ASTEMIZOLE AS A PRN PRODUCT FOR IMMEDIATE RELIEF OF SYMPTOMS.

CONCOMITANT ADMINISTRATION OF ASTEMIZOLE WITH KETOCONAZOLE TABLETS, ITRACONAZOLE, ERYTHROMYCIN, OR QUININE IS CONTRAINDICATED. (SEE CONTRAINDICATIONS AND PRECAUTIONS: DRUG INTERACTIONS.)

SINCE ASTEMIZOLE IS EXTENSIVELY METABOLIZED BY THE LIVER, THE USE OF ASTEMIZOLE IN PATIENTS WITH SIGNIFICANT HEPATIC DYSFUNCTION SHOULD GENERALLY BE AVOIDED.

IN SOME CASES, SEVERE ARRHYTHMIAS HAVE BEEN PRECEDED BY EPISODES OF SYNCOPE. SYNCOPE IN PATIENTS RECEIVING ASTEMIZOLE SHOULD LEAD TO IMMEDIATE DISCONTINUATION OF TREATMENT AND APPROPRIATE CLINICAL EVALUATION, INCLUDING ELECTROCARDIOGRAPHIC TESTING (LOOKING FOR QT PROLONGATION

Patients known to have conditions leading to QT prolongation may experience QT prolongation and/or ventricular arrhythmia with astemizole at recommended doses. The effect of astemizole in patients who are receiving agents which alter the QT interval is unknown. However, in view of astemizole's known potential for QT prolongation, it is advisable to avoid its use in patients with QT prolongation syndrome or who are taking medications which are reported to prolong QT intervals (including probucol, certain antiarrhythmics, certain tricyclic antidepressants, certain phenothiazines, certain calcium channel blockers such as bepridil, and terfenadine), patients with electrolyte abnormalities such as hypokalemia or hypomagnesemia, or those taking diuretics with potential for inducing electrolyte abnormalities.

Rare cases of cardiovascular events have been observed in patients with hepatic dysfunction. Systematic evaluation of the pharmacokinetics of astemizole in patients with hepatic dysfunction has not been performed. Since astemizole is extensively metabolized by the liver, the use of astemizole in patients with significant hepatic dysfunction should generally be avoided.

PRECAUTIONS

General

Caution should be given to potential anticholinergic (drying) effects in patients with lower airway diseases.

Caution should be used in patients with cirrhosis or other liver diseases. (See CLINICAL PHARMACOLOGY section.)

Astemizole does not appear to be dialyzable.

Caution should also be used when treating patients with renal impairment.

Drug Interactions

See CONTRAINDICATIONS and WARNINGS sections for discussion of information regarding potential drug interactions.

Ketoconazole/Itraconazole

Concomitant administration of ketoconazole tablets or itraconazole with astemizole is contraindicated. (See CONTRAINDICATIONS and WARNINGS BOX.)

Due to the chemical similarity of fluconazole, metronidazole, and miconazole IV to ketoconazole, concomitant use of these products with astemizole is not recommended.

Macrolides (Including Erythromycin)

Concomitant administration of erythromycin with astemizole is contraindicated. (See

CONTRAINDICATIONS and WARNINGS BOX.) Concomitant administration of astemizole with other macrolide antibiotics, including troleandomycin, azithromycin, and clarithromycin, is not recommended.

Quinine
Concomitant administration of astemizole with quinine is contraindicated. (See CONTRAINDICATIONS and WARNINGS BOX.)

Information for Patients
Patients taking astemizole tablets should receive the following information and instructions. Antihistamines are prescribed to reduce allergic symptoms. Patients taking astemizole should be advised 1) to adhere to the recommended dose, and 2) that the use of excessive doses may lead to serious cardiovascular events. Some patients appear to increase the dose of astemizole in an attempt to accelerate the onset of action. PATIENTS SHOULD BE ADVISED NOT TO DO THIS and not to use astemizole as a prn product for immediate relief of symptoms. Patients should be questioned about use of any other prescription or over-the-counter medication, and should be cautioned regarding the potential for life-threatening arrhythmias with concurrent use of ketoconazole, itraconazole, erythromycin, or quinine. Human data indicate that although beverages containing quinine (up to 80 mg/day or about 32 ounces of tonic water) may elevate plasma levels of astemizole and desmethylastemizole, this effect is small and is not accompanied by significant prolongation of the QT interval. Patients should be advised to consult the physician before concurrent use of other medications with astemizole. Patients should be questioned about pregnancy or lactation before starting astemizole therapy, since the drug should be used in pregnancy or lactation only if the potential benefit justifies the potential risk to fetus or baby. (See PRECAUTIONS: Pregnancy.) In addition, patients should be instructed to take Astemizole on an empty stomach, e.g., at least 2 hours after a meal. No additional food should be taken for at least 1 hour after dosing. Patients should also be instructed to store this medication in a tightly closed container in a cool, dry place, away from heat or direct sunlight, and away from children.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenic potential has not been revealed in rats given 260x the recommended human dose of astemizole for 24 months, or in mice given 400x the recommended human dose for 18 months. Micronucleus, dominant lethal, sister chromatid exchange and Ames tests of astemizole have not revealed mutagenic activity.

Impairment of fertility was not observed in male or female rats given 200x the recommended human dose.

Pregnancy: ***Teratogenic Effects,*** PREGNANCY CATEGORY C
Teratogenic effects were not observed in rats administered 200x the recommended human dose or in rabbits given 200x the recommended human dose. Maternal toxicity was seen in rabbits administered 200x the recommended human dose. Embryocidal effects accompanied by maternal

toxicity were observed at 100x the recommended human dose in rats. Embryotoxicity or maternal toxicity was not observed in rats or rabbits administered 50x the recommended human dose. There are no adequate and well controlled studies in pregnant women. Astemizole should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Metabolites may remain in the body for as long as 4 months after the end of dosing, calculated on the basis of 6 times the terminal half-life. (See CLINICAL PHARMACOLOGY section.)

Nursing Mothers
It is not known whether this drug is excreted in human milk.

Because certain drugs are known to be excreted in human milk, caution should be exercised when astemizole is administered to a nursing woman. Astemizole is excreted in the milk of dogs.

Pediatric Use
Safety and efficacy in pediatric patients under 12 years of age has not been demonstrated.

ADVERSE REACTIONS

For information regarding cardiovascular adverse events (e.g., cardiac arrest, ventricular arrhythmias), please see CONTRAINDICATIONS and WARNINGS BOX. In some cases, recognition of severe arrhythmias has been preceded by episodes of syncope. Similarly, rare cases of hypotension, palpitations, and dizziness have also been reported with astemizole use, which may reflect undetected ventricular arrhythmia.

The reported incidences of adverse reactions listed in the following table are derived from controlled clinical studies in adults. In these studies the usual maintenance dose of astemizole was 10 mg once daily.

ADVERSE EVENT	Percent of Patients Reporting		
	Controlled Studies*		
	ASTEMIZOLE (N=1630) %	PLACEBO (N=1109) %	CLASSICAL** (N=304) %
Central Nervous System			
Drowsiness	7.1	6.4	22.0
Headache	6.7	9.2	3.3
Fatigue	4.2	1.6	11.8
Appetite increase	3.9	1.4	0.0
Weight increase	3.6	0.7	1.0
Nervousness	2.1	1.2	0.3
Dizzy	2.0	1.8	1.0
Gastrointestinal System			
Nausea	2.5	2.9	1.3
Diarrhea	1.8	2.0	0.7
Abdominal pain	1.4	1.2	0.7
Eye, Ear, Nose, and Throat			
Mouth dry	5.2	3.8	7.9
Pharyngitis	1.7	2.3	0.3
Conjunctivitis	1.2	1.2	0.7
Other			
Arthralgia	1.2	1.6	0.0

* Duration of treatment in Controlled Studies ranged from 7 to 182 Days

** Classical Drugs: Clemastine (N=137); Chlorpheniramine (N=100); Pheniramine Maleate (N=47); d-Chlorpheniramine (N=20)

Adverse reaction information has been obtained from more than 7500 patients in all clinical trials. Weight gain has been reported in 3.6% of astemizole treated patients involved in controlled studies, with an average treatment duration of 53 days. In 46 of the 59 patients for whom actual weight gain data was available, the average weight gain was 3.2 kg.

Less frequently occurring adverse experiences reported in clinical trials or spontaneously from marketing experience with astemizole include: angioedema, asymptomatic liver enzyme elevations, bronchospasm, depression, edema, epistaxis, hepatitis, myalgia, palpitation, paresthesia, photosensitivity, pruritus, and rash.

Marketing experiences include isolated cases of convulsions. A causal relationship with astemizole has not been established.

OVERDOSAGE

In the event of overdosage, supportive measures including gastric lavage and emesis should be employed. Substantial overdoses of astemizole can cause death, cardiac arrest, QT prolongation, torsades de pointes, and other ventricular arrhythmias. These events can also occur, although rarely, at doses (20 to 30 mg) close to the recommended dose (10 mg/daily). (See WARNINGS BOX and DOSAGE AND ADMINISTRATION.)

Seizures and syncope have also been reported with overdose and may be associated with a cardiac event.

Overdose patients should be carefully monitored as long as the QT interval is prolonged or arrhythmias are present. In some cases, this has been up to six days. In overdose cases in which ventricular arrhythmias are associated with significant QT prolongation, treatment with antiarrhythmics known to prolong QT intervals is not recommended. Astemizole does not appear to be dialyzable.

Oral LD_{50} values for astemizole were 2052 mg/kg in mice and 3154 mg/kg in rats. In neonatal rats, the oral LD_{50} was 905 mg/kg in males and 1235 mg/kg in females.

DOSAGE AND ADMINISTRATION

The recommended dosage for adults and children 12 years of age and older is 10 mg (1 tablet) once daily.

DO NOT EXCEED THE RECOMMENDED DOSE. Patients should be advised not to increase the dose of astemizole tablets in an attempt to accelerate the onset of action. (See WARNINGS BOX.) USE OF ASTEMIZOLE IN PATIENTS TAKING KETOCONAZOLE, ITRACONAZOLE, ERYTHROMYCIN, OR QUININE IS CONTRAINDICATED. (See CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS: Drug Interactions.)

Studies evaluating the need for dosage adjustments for patients with hepatic or renal dysfunction have not been performed. Since astemizole is extensively metabolized by the liver, use of astemizole in patients with significant hepatic dysfunction should generally be avoided.

Astemizole should be taken on an empty stomach, e.g., at least two hours after a meal. There should be no additional food intake for at least one hour post-dosing.

HOW SUPPLIED

- Established Name
- Strength of dosage form
- Packaging, NDC number
- Dosage form, shape, color, scoring, imprints
  Note: The innovator's tablet is scored.
- Store at controlled room temperature 15° to 30°C (59° to 86°F). Protect from moisture.
- Dispense in a tight container, as defined in the USP.
- "Caution: Federal Law..." statement.

Include the following information at the end of the HOW SUPPLIED section:

- Date of latest revision.
- "Manufactured by" statement. - Should be consistent with container labels and/or carton labeling.

CONTAINER LABEL

In addition to the general label requirements ("Caution: Federal Law..." statement, statement of net quantity, etc.) please include the following:

Main Panel:

- The established name should read as follows:

  Astemizole Tablets

- If manufacturing multiple strengths, we encourage you to differentiate your product strengths by boxing, contrasting colors or some other means.

Side Panel:

- Dispense in a tight container, as defined in the USP.
- Store at controlled room temperature 15° to 30°C (59° to 86°F). Protect from moisture.
- Usual Dosage: One tablet daily. See package insert.

ADDITIONAL INFORMATION

If manufacturing a unit-of-use container size remember to utilize a CRC closure to comply with the Poison Prevention Act.